



Facultad de Estudios Superiores  
**IZTACALA**

# Endocannabinoid system and eating behavior

## *Sistema endocannabinoide y la conducta alimentaria*

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### **Abstract.**

The objective of this systematic review was to investigate previously published literature that examined the effect of hypercaloric diet on the endocannabinoid system, eating behavior, and the development of obesity. In the present review, we analyzed and described the evidence that suggests that the regulation of the endocannabinoid system through the activation of the receptors for cannabinoid type 1 (CB1R) and type 2 (CB2R) by modulating the production of anandamide, 2- arachidonoylglycerol (2-AG) and oleamide, influence the appetite and satiety centers, inducing or inhibiting the consumption of hypercaloric foods such as Western diet; thereby altering the production of hormones like the ghrelin, insulin, peptide YY and leptin. However, the adequate doses of pure cannabinoids and/or the cannabinoid-enriched Cannabis herbal extracts for the treatment of eating disorders like anorexia and/or obesity, neither for disorders of the mood, have not determined.

**Keywords:** Endocannabinoids; eating behavior; hypercaloric diet; obesity; mood.

**Resumen.**

El objetivo de esta revisión sistemática fue investigar en la literatura publicada previamente acerca del efecto de la dieta hipercalórica sobre el sistema endocannabinoide, el comportamiento alimentario y el desarrollo de la obesidad. En la presente revisión, analizamos y describimos la evidencia que sugiere que la regulación del sistema endocannabinoide modula la producción de anandamida, 2-araquidonoilglicerol (2-AG) y oleamida, y activa los receptores de endocannabinoides tipo 1 (CB1R) y/o tipo 2 (CB2R), influyendo en los centros de control del apetito y la saciedad, de esta forma induce o inhibe el consumo de alimentos hipercalóricos como los que forma parte de la dieta occidental; asimismo, hay alteración en la producción de hormonas como la grelina, la insulina, el péptido YY y la leptina. Sin embargo, hasta el momento no se han establecido las dosis adecuadas de cannabinoides puros y/o extractos herbales enriquecidos de Cannabis para el tratamiento de trastornos alimentarios como la anorexia y/o la obesidad, ni para los trastornos del estado de ánimo.

**Palabras Clave:** Endocannabinoides; conducta alimentaria; dieta hipercalórica; obesidad; estado de ánimo.

## Introduction

Cannabis (or marijuana) contains cannabinoids that are compounds capable of stimulating the endocannabinoid system in humans. Three species of Cannabis have been described: *C. sativa indica* is mainly found in the southern hemisphere of the earth, and this has a higher content of cannabidiol; *C. sativa sativa* is native of Asia, America and Africa, and this is very important and powerful due to its high content of the psychoactive component, tetrahydrocannabinol (THC), in relation to cannabidiol; finally *C. sativa ruderalis*, which is native of southern Siberia and northern Kazakhstan, with low content of THC and a high content of cannabidiol (Fraguas-Sánchez et al., 2014). In general, the flower of the female cannabis plant contains ten times more cannabinoids than the leaf, while stem and seed have lower levels (Sakamoto et al., 1998).

## Material and methods

A systematic review was carried out to describe the effects of hypercaloric diets on the endocannabinoid system, and its relationship with eating behavior and the development of obesity. To do this, a research was performed in PubMed and Scopus databases, and the keywords used were as follows: Endocannabinoids,

cannabinoid type 1 receptor (CB1R), cannabinoid type 2 receptor (CB2R), eating behavior, hypercaloric diet and obesity. No time limit or other exclusion criteria were established. Finally, the articles that, due to their content, contributed to strengthening the subject of the review were selected.

## Results Cannabinoid system

Cannabinoids were originally described in the plant cannabis, and these phytochemicals inhibit or activate the endocannabinoid system. In human, the endocannabinoid system is made up of membrane receptors and their ligands, and the enzymes that synthesize or degrade cannabinoids (Pazos et al., 2005).

### a). Cannabinoid receptors

In mammals, there are two receptors for cannabinoids, the CB1R and CB2R, where the CB1R is found in greater quantity in the cerebellum, hippocampus and basal ganglia, and it is also expressed in the gastrointestinal tract, adipose cells, liver parenchyma and skeletal muscle. The CB2R is widely expressed in the cortex, nucleus accumbens, hippocampus, striatum, thalamus, hypothalamus, cerebellum, and in peripheral tissues and in the immune system (Guindon & Hohmann, 2009).

### b. cannabinoids

The best known and most studied phytocannabinoids are delta-9- tetrahydrocannabinol or tetrahydrocannabinol ( $\Delta^9$ -THC or THC, respectively), which is the psychoactive component and is due to its classification as a “drug”; the second component is cannabidiol (Fig. 1) (Franco et al., 2020). In humans, the main endocannabinoids are anandamide (AEA), 2-arachidonoylglycerol (2-AG), and oleamide (Fig. 1) (Di Marzo et al., 2004).

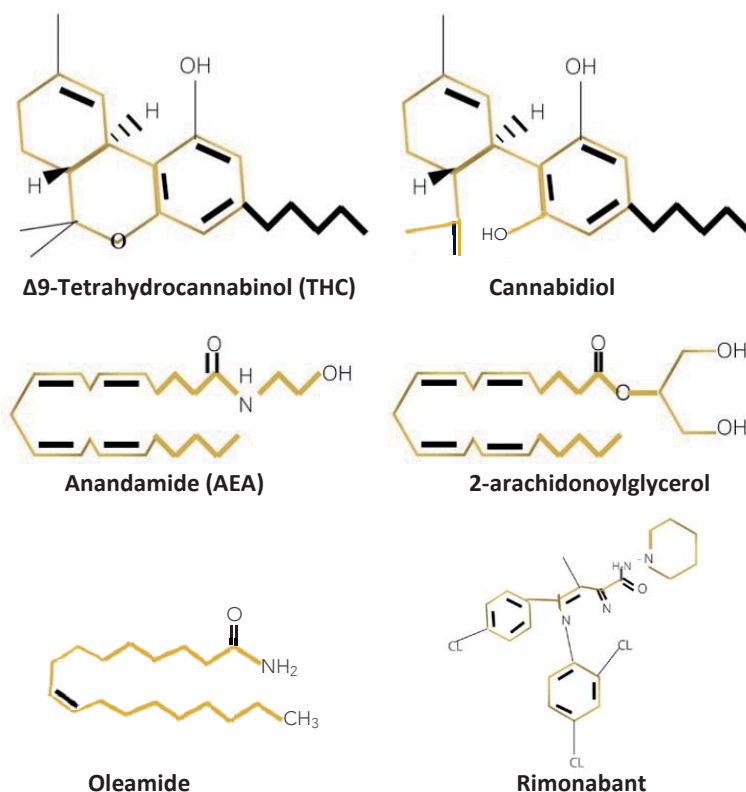
### c. Enzymes involved in the metabolism of cannabinoids

The synthesis of 2-AG and AEA appears to occur through different pathways that remains to be completely understood. It has been proposed that postsynaptic activation of the metabotropic glutamate receptor 1 and 5 (mGluR1 and mGluR5; these are G-protein-coupled receptor) active the phospholipase C (PLC) and/or phospholipase D (PLD), mediating the hydrolysis of membrane lipids; then the activation of

phospholipase A (PLA) produces lysophospholipids like arachidonoyl and others. The 2-AG can be synthesized by dephosphorylation of arachidonoyl by the lysophospholipase C. For its part, the N-arachidonoyl phosphatidylethanolamine (NAPE) is synthesized from the phosphatidylethanolamine and arachidonoyl-phospholipid by the N-acyltransferase; then the enzyme N-acyl-phosphatidylethanolamine phospholipase D (NAPE-PLD) hydrolyzes NAPE to yield AEA and phosphatidic acid (Puente et al., 2011).

It is important point out, that the inhibition of mGluR5 by using the negative allo- steric modulator (VU0409106) induced a reduction of food intake, body weight, and adipose tissue inflammation in mice treated with high-fat diet (HFD). Moreover, the negative modulation of mGluR5 also was associated with a decrease of the binge- like eating, the most common type of eating disorder (Oliveira et al., 2021). More important, that the activation of mGluR1/5 in the rat hypothalamus increase food intake through the increase of 2-AG, which was prevented by AM251

Figure 1. Chemical structures of cannabinoids and rimonabant.



(CB1 inverse agonist). These data suggest the potential interaction between the glutamatergic and cannabinergic systems in promoting food intake (Sanchez-Fuentes et al., 2016).

In the other hand, anandamide is rapidly degraded by the fatty acid amide hydrolase (FAAH) to produce arachidonic acid and ethanolamine or monoacylglycerol (Cravatt et al., 1996). It has also been described that in the terminal stria, the entry of calcium induces the production of 2-AG, which is degraded by the enzymes diacylglycerol lipase-alpha (DAGL alpha) and beta (DAGL beta) to arachidonic acid and glycerol. Moreover, the 2-AG can be degraded by the cyclooxygenase 2(COX2) and lipoxygenases to produce prostaglandin E2 glyceryl ester and 12-hydroperoxyeicosa-5,8,10,14-tetraenoic acid glyceryl ester, respectively (Cravatt et al., 1996; Dinh et al., 2002).

## Regulation of appetite and satiety

The regulation of food intake is usually divided into homeostatic feeding, that aims to maintain the body weight and metabolic function, and hedonic feeding, which is primarily driven by sensory perception or pleasure (Rocheffort et al., 2021). Hedonic regulation is given by sensory and rewarding stimuli, which can prevail over the homeostatic control, leading to excessive consumption of high-palatability food, even when energy requirements have been met, contributing to weight gain and obesity (Díaz-Rúa et al., 2020). The hypothalamus is the main region of the brain that regulates appetite and food intake, depending on the caloric and nutritional requirements of the entire body. More specifically, the arcuate nucleus, hypothalamic ventromedial nucleus, hypothalamic lateral nucleus, paraventricular nucleus, and dorsomedial nucleus participate in the regulation of appetite and satiety; in addition to the nucleus accumbens, the nucleus of the solitary and parabrachial tract of the brainstem, and various structures of the cerebral cortex (Berthoud, 2002). The stimulation of the hypothalamus lateral nuclei produces hyperphagia, and removal of the lateral hypothalamus blocks or decreases the desire to consume food. For their part,

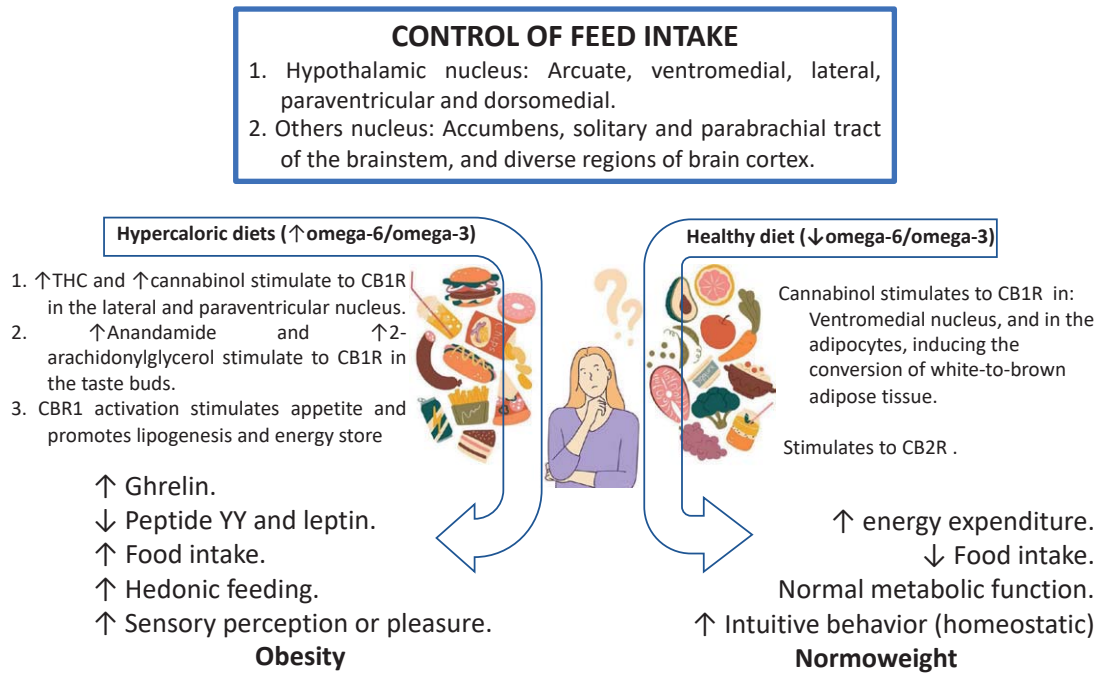
the ventromedial nuclei play an important function in satiety, they participate in or induce a state of nutritional satisfaction, which decreases or represses the hunger center. Electrical stimulation of satiety centers, in animal models, induces rejection of the food and aphagia (Berthoud, 2002; Broberger, 2005).

It is important to consider that the CB1R modulates the taste and smell pathways and increases the food palatability (Muguruza et al., 2019), and also stimulates the appetite-related brain centers, causing hyperphagia and favoring the accumulation of adipose tissue (Fig. 2) (Clark et al., 2018). In animal models, the activation of CB1R in the hypothalamus induces a strong stimulation of the consumption preferably of foods rich in fat, and induces the lipogenesis in liver, and increases the body weight gain (Clark et al., 2018). Muguruza et al described in mice that the CB1R is involved in the motivation for appetizing foods (Muguruza et al., 2019). In addition, rainbow trout (*Oncorhynchus mykiss*) that were fed a high-fat diet consumed more feed compared to those fed a control diet, which was attributed to food palatability. Increased consumption of the high-fat diet was accompanied by higher levels of anandamide and 2-AG in serum and in the hypothalamus, and in the telencephalon, which is a region involved in hedonic responses in fish (Díaz-Rúa et al., 2020). This is consistent with what was observed in humans, where the inhibition of the CB1R by the antagonist rimonabant (Fig. 1), decreased appetite and was beneficial in the treatment of obesity, but the rimonabant was withdrawn due to serious side effects on mood state in human (Van Gaal et al., 2005).

## Cannabinoid system and eating disorders

Today the prevalence of eating disorders has significantly increased in both male and female, and these disorders often arise from underlying problems such as anxiety, de-pression, and/or body dysmorphic disorder. Unfortunately, the eating disorders have been known to be complicate to treatment, and these are disabling and costly mental disorders

**Figure 2. Proposed mechanism of the participation of cannabinoid system in the control of appetite and food intake. THC, tetrahydrocannabinol; CB1R y CB2R, receptors for cannabinoids type 1 and 2; omega-6/omega-3, polyunsaturated fatty acid omega-6 y 3.**



that considerably impair physical health and disrupt psychosocial functioning, and these can be deadly. Eating disorders including anorexia nervosa, bulimia nervosa, binge eating disorder, eating disorders not otherwise specified, and night eating syndrome (Avraham et al., 2017a; Zam et al., 2018). First, anorexia nervosa is a potentially severe, chronic, and relapsing mental disorder that can affect to men and women of all ages, races, and from all social classes, however, adolescent girls and young adult women are particularly at risk. Anorexia nervosa is associated with suicide and mortality linked with the physical consequences of starvation. Second, bulimia nervosa is a multifactorial health disorder characterized by a disturbed self-perception of body weight and shape and therefore by cycles of binge eating followed by compensatory behaviors such as self-induced vomiting; whereas that in persons with non-purging bulimia uses other inappropriate methods of compensation for binge episodes, such as excessive exercising or fasting. Third, the binge eating disorder is when

individuals experience a loss of control over one's eating behavior, consuming an amount of food that is really larger than what most people would eat in a similar period of time under similar circumstances. Fourth, eating disorders not otherwise specified are disorders that do not meet the criteria for any other specific eating disorder, and represent about 50% of all eating disorders, and if the disordered behaviors continue, they may progress to frank anorexia nervosa or bulimia nervosa. Fifth, night eating syndrome is a disorder strongly related to overweight and obesity. This syndrome is characterized by recurrent episodes of night eating, which is described as either excessive food consumption in the evening (evening hyperphagia). Moreover, it has been reported that persons with this syndrome consumed a large majority of their caloric intake (25% or more) at night (Avraham et al., 2017b; Zam et al., 2018).

The eating disorders involve disturbed attitudes towards weight, body shape, and eating. Individual psychological traits, as well as emotional and cognitive

components, are determinants of eating behaviors, and research carried out in recent years suggest of a key role for the endocannabinoid system in regulating these behaviors. For example, a more positive behavior that predisposes individuals to eat according to their physiological needs, that is, a more intuitive behavior that promote healthier eating, is associated with plasma levels of 2- eicosapentaenoyl-glycerol and 2-docosapentaenoyl-glycerol, derivatives from omega-3 polyunsaturated fatty acids. These findings suggest that the endocannabinoid system participates in intuitive behavior, and that the consumption of omega-3 can increase the synthesis of these cannabinoids, inducing a state of satiety (Fig. 2). A pilot study conducted in women with anorexia nervosa found that these women were less hungry than women without anorexia during fasting and after eating. In addition, women with anorexia nervosa had significantly lower plasma levels of anandamide compared to controls both fasting and after eating. While the plasma levels of 2-AG were similar in both groups of women (Piccolo et al., 2020). Consistent with the above result, in addicted people, marijuana abstinence produces anorexia (Haney et al., 1999a, 1999b). In this regard, it has been reported that women with anorexia who were administered 2.5 mg of the synthetic cannabinoid (Dronabinol, twice a day for 4 weeks), gained 730 g of body weight compared to patients who took placebo (Andries et al., 2014). Another study reported that in women with anorexia nervosa who were treated with 1 mg of THC per day for one week and 2 mg per day for 3 weeks, the THC improved psychic symptoms. Additionally, the women showed a significant increase in body care, and diminution of the negative emotions, such as inefficiency, asceticism, and depression (Avraham et al., 2017a). This suggests that in people with anorexia there is a decrease in THC levels, and the THC administration increases appetite and food consumption, as well as improves mood (Fig. 3). Interestingly, Gérard et al. (2011) administered a radioactively labeled agonist to women with anorexia and bulimia, and they followed it in the brains using positron emission tomography (PET). The women with anorexia nervosa had an increase of CB1R in cortical and subcortical regions of the brain, whereas both bulimic and anorexic women exhibited

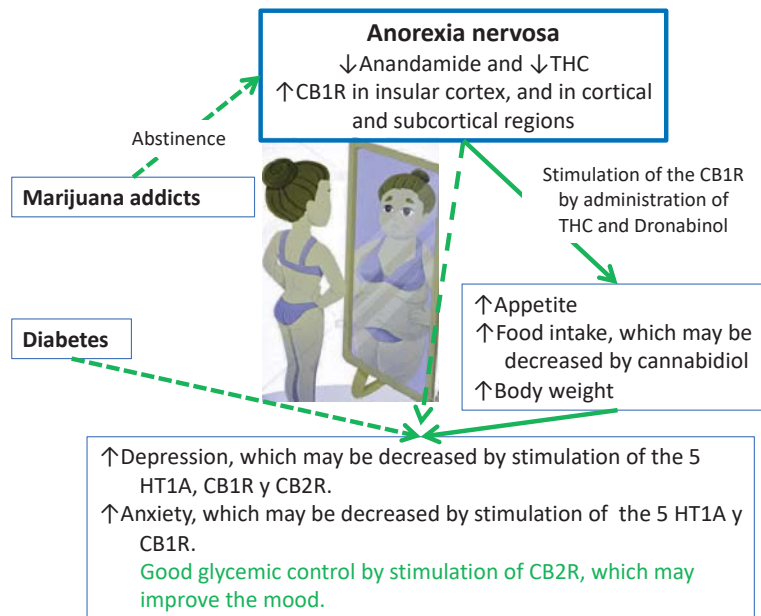
significantly higher CB1R density in the insular cortex (Gérard et al., 2011). It is worth mentioning that Miederer et al. determined the distribution of CB1R in the brain of young adult mice, using the agonist [<sup>18</sup>F] MK-9470 and monitoring by PET. It was confirmed that the CB1R is distributed in the brain, and that there is a higher expression in regions such as the telencephalon, diencephalon, midbrain, and hindbrain in healthy adult mice (Miederer et al., 2020). Casteels et al. corroborated the involvement of the CB1R in mood disorders in a rat model of anorexia nervosa and performed in vivo brain mapping using the CB1R ligand [<sup>18</sup>F]MK- 9470 and following the signal by PET; it was found that female rats have affected the CB1R mainly in the hippocampus, which was reversible after disappearance of the anorexia nervosa (Casteels et al., 2014). Moreover, Chaves et al. described that cannabidiol treatment decreases depression and anxiety in streptozotocin-induced diabetic rats. This was demonstrated by administering the serotonin (5-hydroxytryptamine 1A, 5HT1A) receptor antagonist (WAY100635, 0.1 mg/kg, i.p.), the CB1R antagonist (AM251, 1 mg/kg, i.p.), or the CB2R antagonist (AM630, 1 mg/kg, i.p.) to diabetic rats before administration of cannabidiol (30 mg/kg, i.p.). Interestingly, the anti-anxiolytic effect is mediated by the 5 HT1A and CB1R but not by the CB2R, while the antidepressant effect was mediated by the serotonin receptor 1A, and the CB1R and CB2R (Chaves et al., 2021).

Taken together, the above findings support that CB1R has important implications for mood disturbances such as depression and anxiety observed in persons with anorexia nervosa, and that other receptors, such as CB2R and serotonin 5HT1A, appear to also participate in these alterations (Fig. 3).

## Effects of cannabinoids on the food intake and development of obesity

It has also been suggested that endocannabinoid system promotes hedonic eating, contributing to obesity epidemic in humans. In this respect, studies in healthy human adults, the variations in the 2-AG and 2-oleoyl-glycerol levels in serum were lower during the day in obese people compared to those with normal weight,

**Figure 3. Proposed mechanism between cannabinoid levels and mood disturbances in women with anorexia. THC, tetrahydrocannabinol; CB1R y CB2R, receptors for cannabinoids type 1 and 2; 5HT1A, receptor for 5-hydroxytryptamine 1A.**



as well as the maximum peaks in these levels were delayed 4 to 5 hours in obese people. Additionally, it was described that cortisol levels were similar between obese and non-obese people. These results suggest that in obese people, there is a decrease and a delay in the maximum peaks of serum 2-AG and 2-oleoylglycerol compared with the circadian clock synchronization in nonobese people (Hanlon et al., 2020).

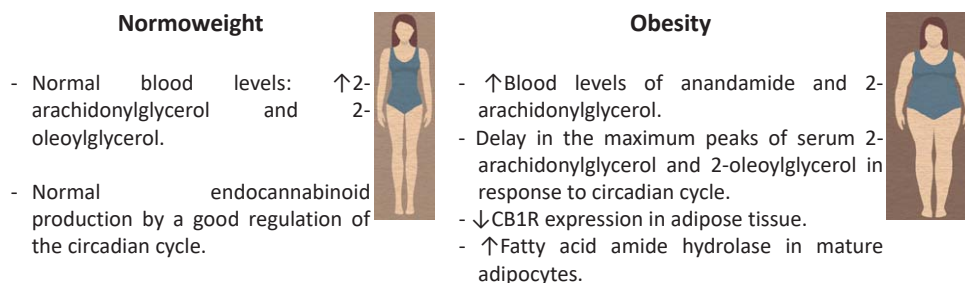
Engeli et al. reported that obese women have 35% and 52% higher circulating levels of anandamide and 2-AG, respectively, compared to lean women. In subcutaneous adipose tissue, obese women also showed a 34% reduction in CB1R mRNA and a 59% reduction in FAAH mRNA compared with non-obese women. Moreover, in obese women, the expression of the CB1R and the FAAH was increased in mature adipocytes compared to preadipocytes (Fig. 4) (Engeli et al., 2005). First, these results suggest that in obese women, the expression of the CB1R and the FAAH increase with the maturation of the preadipocyte, but do not explain why the reduction of these markers in subcutaneous adipose tissue.

Second, the reduction in expression of the CB1R in adipose tissue is consistent with the increase in

circulating levels of anandamide and 2-AG, because if there is a reduction of the receptor, it requires higher amount of cannabinoids to achieve the same response; however, the increased expression of FAAH in adipose tissue is contrary to expectations, but the enzyme activity was not determined. In addition, Yagina et al. (2020) showed that women with binge eating disorders have also higher levels of anandamide, 2-AG, leptin, and insulin compared to women without the binge eating disorder (Yagin et al., 2020).

In rats, the direct administration of THC into the hypothalamic paraventricular nucleus activates CB1R and produces stimulation of appetite, this stimulation is blocked by the direct administration of 0.1 µg of the CB1R antagonist, AM251 [N-(piperidin-1-yl)-5-(4-iodophonyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide] (Cruz-Martínez et al., 2010). This may explain why most people who smoke cannabis often have increased appetite, which may be due to the THC content. This is also supported by Dong et al. in diabetic KKAY mice, where treatment for 3 weeks with the CB1R antagonist (LH-21) significantly decreased blood pressure, body weight, and white adipose tissue content, and slightly decreased the food

**Figure 4. Blood and adipose tissue profile of cannabinoids and their receptors in persons with normal weight and established obesity.**



intake. In addition, the expression of the adipokines (lipocaline- 2, leptin) mRNA was decreased in white adipose tissue, which was consistent with a reduction in serum levels of inflammatory cytokines (TNF- $\alpha$ , IL-6 and CXC-1), and lipocalin-2 and leptin (Dong et al., 2018). However, it is important to note that another study showed that in high-fat diet-induced obese mice, the administration of THC (2 mg/kg for 3 weeks follow for 4 mg/kg for a further week) reduced food intake, weight gain, and induced changes in the intestinal microbiota of obese mice, in the sense of being more similar to the non-obese control mice; however, the chronic administration of THC did not have these beneficial effects (Cluny et al., 2015).

On the other hand, cannabidiol and cannabinol have been suggested to have opposite effects on feed intake. In this regard, oral treatment of rats with cannabinol stimulated the CB1R and increased food consumption, while cannabidiol significantly reduced food consumption during the test period.

Cannabigerol administration did not induce changes in eating behavior (Farrimond et al., 2012). These results are consistent with some studies of humans who consume Cannabis, they showed a decreased desire to eat, hunger and prospective food consumption and an increased satiety (Sansone & Sansone, 2014), likely due to a higher concentration of cannabidiol (Fig. 2).

Taken together, the above findings suggest that CB1R stimulation is involved in the control of appetite and white adipose tissue content, as well as the expression of proinflammatory molecules, and is dependent on the agonist that stimulates the CB1R

and/or CB2R and in which tissue stimulates it, then a response of increased appetite or decreased appetite will predominate (Fig. 2).

Interestingly, in 3T3-L1 adipocyte cultures, cannabidiol induces the conversion of white-to-brown adipose tissue, and thereby increases the calorie burning. This was evidenced by increased expression of the *Ucp1*, *Cited1*, *Tmem26*, *Prdm16*, *Cidea*, *Tbx1*, *Fgf21*, and *Pgc-1 $\alpha$*  genes, and of the *UCP1*, *PRDM16*, *SIRT1*, *PLIN* and *PGC-1 $\alpha$*  proteins in brown fat tissue (Parray & Yun, 2016). Additionally, the administration of anandamide or 2-AG to mice increased the gustatory nerve response to sweeteners without affecting the responses to salty, acidic, bitter and umami compounds, but mice knockout of the CB1R did not show changes. It is worth mentioning that the CB1R is present in type II taste cells and its stimulation by the cannabinoids used is inhibited by the CB1R antagonist (AM251) but not by the CB2R antagonist (AM630) (Yoshida et al., 2010). This suggests that stimulation of the CB1R in the taste buds contributes to body weight gain by stimulating food intake and hedonic eating (Fig. 4).

Some hormones are also affected by THC administration, affecting signaling pathways related to the food intake (Gatta-Cherifi et al., 2012; Riggs et al., 2012); this is thanks to leptin and insulin that stimulate the arcuate nucleus, carrying information about the state of the energy deposits found in fatty tissue, and as well as by the ghrelin production in the stomach during the fasting state. In this way, the increased release of ghrelin increases appetite by stimulating the arcuate nucleus via humoral, through the *vagus*



nerve (Fig. 2). This is supported by a study conducted in patients positive for the human immunodeficiency virus (HIV), where the patients received THC for smoking Cannabis, and they presented a significant increase in plasma ghrelin levels, concomitant with a decrease in peptide YY and leptin levels, and without changes in serum insulin levels in compared to controls who received placebo (Riggs et al., 2012). In addition, it was reported that there is a correlation between the THC and leptin levels in human serum, having higher levels of THC and lower levels of leptin (Gatta-Cherifi et al., 2012; Riggs et al., 2012). For their part, Farokhnia et al. observed that in young subjects who smoked Cannabis ( $6.9 \pm 0.95\%$  of THC, corresponding to  $\sim 50.6$  mg) had decreased plasma levels of insulin and glucagon-like peptide 1 (GLP-1) compared to subjects who received placebo. In addition, subjects who consumed Cannabis orally had decreased levels of ghrelin compared to control subjects who received placebo (Farokhnia et al., 2020).

Contradictorily, the stimulation of CB<sub>1</sub>R in pancreatic  $\beta$  cells in vitro increases insulin release and thus glucose uptake (Matias et al., 2006), which suggests that there should be an increase in live weight but let us take into account that this finding was performed in cells in culture and does not necessarily represent the effect in vivo.

In a pilot study in healthy subjects, pleasure eating was found to increase blood levels of the ghrelin and 2-AG; while the levels of anandamide, oleoylethanolamide, and palmitoylethanolamide progressively decreased after consumption of both highly pleasurable and unpleasant isoenergetic foods (Monteleone et al., 2012). What was previously observed for ghrelin agrees with that reported by Ching-Heng et al., who observed that rats increase food consumption by administering ghrelin ( $0.1$  mol/rat in  $10$  microL of saline solution by the i.p. route). In addition, administration of the CB<sub>2</sub>R antagonist (AM630,  $1$  mg/kg i.p.) also increased food consumption in rats, while administration of the CB<sub>1</sub>R antagonist (AM-251,  $1$  mg/kg i.p.) decreased consumption. Concordantly, administration of the CB<sub>1</sub>R antagonist blocked the increase in food consumption induced by ghrelin administration, but there was no effect of the CB<sub>2</sub>R antagonist. The above results demonstrate that the CB<sub>2</sub>R is involved in the inhibition

of food intake and satiety, while the CB<sub>1</sub>R promotes food intake in the fasting condition (Fig. 2). Moreover, the induction of feeding by ghrelin is a CB<sub>1</sub>R-dependent mechanism (Ching-Heng et al., 2015).

## Impact of dietary omega-6/omega-3 ratio on the endocannabinoid system

A high ratio of omega-6/omega-3 (w-6/w-3) fatty acids strongly contributes to the metabolic dysregulation associated with the modern Western diet (Brown et al., 2013; Cordain et al., 2005; Murray et al., 2018; A. P. Simopoulos, 2002). The Western diet, characterized by a high ratio of w-6/w-3, leads to a chronic overstimulation of the CB<sub>1</sub>R and thus obesity (Freitas et al., 2018; Artemis P. Simopoulos, 2016). Both w-6 and w-3 fatty acids compete for the same enzymes, when the amount of w-6 is proportionally greater than the amount of w-3, most of those enzymes may use w-6 fatty acids. This causes an abnormal increase in anandamide and 2-AG, resulting in overstimulation of CB<sub>1</sub>R. Elevated CB<sub>1</sub>R activity, in turn, causes increased food intake and excessive energy storage and conservation, leading to an increase of the adipose tissue content (Fig. 4). Therefore, an increase of the consumption of w-3 fatty acids could represent a powerful and interesting treatment against obesity, since it could decrease the synthesis of the anandamide and 2-AG, and at the same time could decrease the expression of the CB<sub>1</sub>R, which leads to reduced sensitivity to anandamide and 2-AG (Clark et al., 2018).

## Conclusions

The regulation of the endocannabinoid system influences appetite and food intake, which may increase the consumption of hypercaloric foods such as the Western diet, since it likely induces an increase in hormones levels such as ghrelin and insulin, and decreases peptide YY and leptin. In addition, it is important to establish adequate doses of pure cannabinoids and/or when a cannabis plant part is used for the treatment of eating dis-orders ranging from anorexia to obesity.

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